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ABSTRACT

This paper categorizes the many benefits of physical activity, offering information concerning the type of dose necessary to get that benefit. In 2000, Health Canada and the United States Centers for Disease Control and Prevention, along with other agencies, sponsored a symposium to determine whether there was a dose-response relationship between physical activity and several health related outcomes. A group of 24 experts from six countries reviewed the published research on several health outcomes (all-cause mortality, cardiovascular disease, type 2 diabetes mellitus, cancer, blood pressure, body weight and body composition, bone density, blood lipids and lipoproteins, hemostatic factors, low back pain and osteoarthritis, and quality of life and independent living in the elderly, depression, and anxiety. Results showed ample evidence supporting the beneficial effects of regular physical activity on all reviewed health outcomes. There was a strong suggestion of an inverse and linear relationship between regular physical activity and rates of all-cause mortality, total cardiovascular disease, coronary heart disease incidence and mortality, and incidence of type 2 diabetes mellitus. For other health outcomes, the dose-response relationship with physical activity was less clear. (Contains 15 references.) (SM)

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Dose-Response Issues Concerning the Relations Between Regular Physical Activity and Health

Tuomo Rankinen and Claude Bouchard

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President's Council on Physical Fitness and Sports

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Dose-Response Issues Concerning the Relations Between Regular Physical Activity and Health

A Note from the Editors

Ample evidence is now available to show that regular physical activity has many health benefits. It is also clear that the amount of activity necessary to produce one benefit may be quite different from the amount necessary for producing another. In question is just how much activity (how big of a dose) is necessary to produce a given specific benefit (response). As editors we asked two of the leading experts in the field (Drs. Tuomo Rankinen and Claude Bouchard) to prepare this issue of the *Digest*. These authors were chosen because of their extensive involvement in the study of dose/response issues. The authors categorize the many benefits of physical activity and present information concerning the type of dose necessary to get that benefit. As the reader will see, some benefits require a heavy dose of activity while other benefits may result from more moderate doses. For some benefits, more evidence will be necessary to determine how much activity is necessary for achieving a benefit.

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Introduction

The beneficial effects of regular physical activity on primary and secondary prevention of several common chronic diseases are well recognized and reduction of sedentary living is one of the cornerstones of contemporary public health programs. For instance, the American Heart Association added physical inactivity on the list of major cardiovascular risk factors in 1992 and federal agencies such as the CDC, the Surgeon General, the PCPFS, and the NIH have recommended to the public to be physically active on a regular basis. Although the positive health effects of physical activity have been widely accepted, the issue of the relation between the amount of physical activity and the health benefits remains controversial. In October 2000, Health Canada and the United States Centers for Disease Control and Prevention along with other agencies sponsored a Consensus Symposium to determine whether there is a dose-response relationship between physical activity and several health-related outcomes and to identify areas for future research[1]. Participation was by invitation and 24 experts from six countries were asked to review the evidence. The published research was evaluated according to an evidence-based methodology. The Consensus Committee consisted of individuals with experience and knowledge in medicine and public health, but who were not engaged in physical activity research. They reviewed and evaluated the evidence presented, and for each health benefit assigned an evidence category ranging from A (rich body of evidence) to D (consensus of experts) (see Table 1 for details). The group also identified topics for future research[5]. The proceedings of this Consensus Symposium provide the material for this issue of the PCPFS *Research Digest*.

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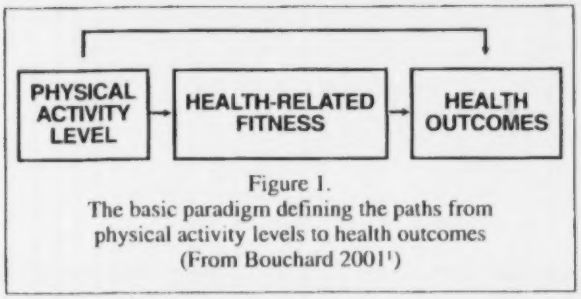

Figure 1.
The basic paradigm defining the paths from physical activity levels to health outcomes
(From Bouchard 2001[1])

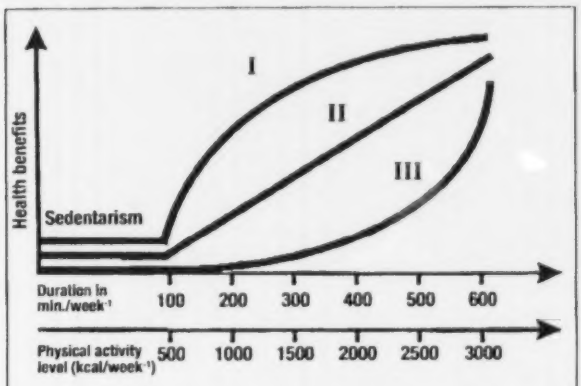

Figure 2.
Schematic illustration of the relationships between physical activity level and health outcomes
(from Bouchard 2001[1])

Background

The emphasis of the Symposium was on the level of physical activity necessary to achieve specific health outcomes. The basic paradigm underlying the consensus effort defined two paths that link physical activity to health outcomes (Figure 1). The first one is a path in which changes in physical activity level affect health directly. The second path is an indirect one, i.e., it assumes that variation in physical activity level induces changes in health-related fitness, which in turn influence health outcomes. The main challenge of the Consensus Committee was to define the nature of the relationship between regular physical activity and various health endpoints. A considerable body of evidence shows that all health outcomes do not respond in the same manner to an increased level of physical activity. Three potential models for the physical activity/health benefit relationships are depicted in Figure 2. Curve II illustrates a relationship where health benefits increase linearly as a function of increasing physical activity level. An example of this type of curve is the apparent association between physical activity and mortality rates. The greater the dose, the greater the response. Curve I represents non-linear relationships, where health benefits are obtained from low to moderate levels of activity. Curve III represents a non-linear relationship where health benefits are obtained from high levels of activity. The association between physical activity and blood pressure/hypertension is an example of a relationship following Curve I, which indicates that the greatest health benefits are obtained from low to moderate levels of physical activity and further increase in volume or intensity of activity does not provide significantly greater additional benefits. The current physical activity recommendations are based on a dose-response pattern described by Curve II, and one of the aims of the Consensus Symposium was to examine critically the evidence in support of this dose-response pattern.

A prerequisite for the assessment of a dose-response relationship between physical activity and health outcome is an appropriate measurement of physical activity level. Ideally, information on frequency and duration (time) and intensity (absolute and relative) of activities should be available to calculate the dose (or volume) of exercise. The dose can be defined as the energy expended in physical activity. The Consensus Committee considered the currently used field methods (questionnaires, activity records, recall diaries) as too imprecise for dose-response studies[5]. Since these methods are based on self-reports, the inter-individual differences in the perception and reporting of the intensity of physical activities induce considerable error in the energy expenditure estimates. Furthermore, the intensity estimates may further vary across age and sex groups as well as between lean and obese. However, for historical reasons, a substantial fraction of the studies that have addressed dose-response issues are based on such methods.

Ideally, the assessment of the dose-response relationship between physical activity and health outcomes should be based on data from several randomized controlled trials (RCTs). However, such data are not always available, and in some cases RCTs cannot even be contemplated. For example, an RCT to study the effects of physical activity on mortality would not be feasible due to financial and practical reasons. In such cases, we have to rely on other lines of evidence and on the degree of concordance or discordance among variety of study designs, such as non-

randomized controlled trials, prospective and cross-sectional observational studies, case studies and animal studies. Table 1 describes the four classifications of evidence that will be used in the remainder of this paper. The richness of the evidence varies across classifications, but all four categories provide different, but useful, evidence. It is also important to consider the increased risk of adverse events associated with increased volume and intensity of exercise when investigating the dose-response relationship between physical activity and health outcomes. Because of the increasing risk of adverse events, the net benefit of higher levels of physical activity may not be as great as predicted.

Table 1.
The evidence categories with the sources of evidence

Evidence Category	Sources of Evidence
A	Randomized controlled trial (rich body of data)
B	Randomized controlled trial (limited body of data)
C	Non-randomized trials (observational studies)
D	Committee consensus judgment

For detailed description of the evidence categories, see Bouchard 2001[1]

Dose-Response in Physical Activity and Health Outcomes

Mortality and morbidity

All-cause mortality

An impressive amount of data are available from observational studies on the dose-response relationship between physical activity or cardiorespiratory fitness and all-cause mortality and cardiovascular disease mortality (Evidence Category C)[7,8]. A total of 44 studies investigating all-cause mortality were identified, with 38 assessing physical activity, five physical fitness, and one both. The majority of the physical activity studies dealt with leisure-time activities, three investigated work-related activity and nine studies assessed both. Most of these studies demonstrated a dose-response relationship between the volume of physical activity and all-cause mortality rates[8]. The Panel concluded that there is Category C evidence for a dose-response relationship between the volume of physical activity and all-cause mortality in adult men and women of all ages from Europe and the United States. The inverse relationship seems to be linear (Line II in Figure 1) although the slope needs to be further refined. Moreover, the minimal effective dose remains to be defined, but an activity-related energy expenditure of 500 kcal/week appears to have a slight favorable effect and one of 1000 kcal/week is associated with a 30% reduction in all-cause mortality rates[5,8].

Cardiovascular disease

A similar inverse dose-response relationship has been observed between physical activity and both the incidence and mortality rates from cardiovascular and coronary heart disease[7]. The association has been demonstrated both for the volume and intensity of physical activity. The relationship appears to be linear when reported in terms of relative risk, and although the majority of the studies have been done in men, the association seems to be similar in women. The Consensus Committee concluded that Category C evidence supports an inverse and linear dose-response relationship between physical activity and both the incidence and mortality rates from all cardiovascular and coronary heart disease[5]. The evidence for a dose-response relationship between physical activity and incidence and mortality rates from stroke is less consistent than that for cardiovascular disease. Several observational studies have reported that both low and high levels of physical activity are associated with increased stroke risk (U-shaped relationship), although the lack of detailed information on the type of stroke (hemorrhagic vs. ischemic) hinders the interpretation of these results[7].

Type 2 diabetes mellitus

There is strong epidemiological evidence supporting the protective effect of physical activity against type 2 diabetes mellitus and the data support a dose-response relationship (Category C). Likewise, Category C evidence was concluded for a dose-response relationship between physical activity and CVD and all-cause mortality in type 2 diabetics. The beneficial effects of physical activity, both alone and in combination with dietary intervention, in the prevention of transition from impaired glucose tolerance to type 2 diabetes have now been clearly recognized[4,5]. Two large diabetes prevention trials[6,14] were published after the Consensus Symposium, both providing strong evidence that life style modification, including increased physical activity level, prevents or delays the

development of type 2 diabetes mellitus in subjects with impaired glucose tolerance. It would appear now that the level of evidence for a role of regular physical activity in the prevention of type 2 diabetes is closer to Category A.

Relatively large clinical trials have shown a positive effect of exercise training on glucose homeostasis in type 2 diabetics[4]. Improvements in blood glucose levels and in %HbA1c have been generally modest, yet clinically important. In most of the studies, the exercise-specific effect on glucose metabolism is difficult to separate from the effects of diet and medication. The Consensus Committee concluded that there is Category B evidence supporting the beneficial effects of exercise training on glucose homeostasis in patients with type 2 diabetes but evidence for a dose-response relationship is still inconclusive[4].

Cancer

Data from observational studies suggest that overall cancer incidence and mortality rates are lower in physically active individuals as compared to sedentary subjects, although differences in diet and other health behaviors confound the interpretation of these studies[13]. The best evidence has been reported for colon cancer incidence, for which 71% of the 49 reviewed studies show an inverse relationship with physical activity. Twenty of these studies showed evidence of a dose-response relationship, but since most compared only two activity levels, the evidence was considered to be moderate (Category C). Moreover, due to missing data on the volume of physical activity, it was not possible to determine the shape of the dose-response curve. The evidence for the relationship between physical activity and other types of cancer was found to be conflicting[5,13].

Biological risk factors

Blood pressure

Results of a meta-analysis summarizing 44 randomized clinical trials show that mild to moderate intensity aerobic training reduces systolic blood pressure 2.6 and 7.7 mmHg and diastolic blood pressure 1.8 and 5.8 mmHg in normotensives and hypertensives, respectively. The data also indicate that training intensity and time per session are not significantly related to net changes in SBP and DBP, whereas duration of the training program is associated with changes in SBP, but not in DBP. Dose-response issues on blood pressure response to training were addressed in nine RCTs. These studies indicate that endurance training at 50% or 75% of maximal is equally effective in reducing blood pressure levels[3]. Thus, the Consensus Committee concluded that there is Category A evidence from RCTs to support the effectiveness of moderate intensity (50% of maximal exercise tolerance) endurance training in reducing blood pressure (similar to Line I, Figure 1). Training at high-intensity level seems to provide no additional benefits, although data on this question are still scarce[5].

Body weight and body composition

Evidence for a linear relationship between physical activity-induced energy expenditure and amount of weight loss from short-term (≤ 16 weeks) studies with controlled diets was considered strong enough to warrant a Category A classification[11]. However, the evidence was much less strong for long-term (≥24 weeks) studies. Data on physical activity and abdominal fat loss (independent of weight loss) were deemed too scarce to evaluate and establish a dose-response relationship, although visceral fat loss was considered to be comparable in diet and exercise-based intervention studies (Category B)[11]. The Panel found some merit for the hypothesis that physical activity is associated with the prevention of weight gain over time, but due to the observational nature of the data, the dose-response question remains unclear (Category C). The Consensus Committee also pointed out that the majority of the data are derived from middle-aged Caucasian males and, therefore, research on the dose-response relationship between physical activity and body composition should be expanded to women and other ethnic groups[5].

Boné density

The evidence that physical activity is effective in maintaining bone mass in premenopausal women and in decreasing bone loss after the menopause was found to be convincing (Category A)[15]. Although no data are available on the dose-response relationship, it seems that the beneficial effect of exercise on bone mass is related to high-intensity activities. Data regarding the role of exercise on peak bone mass are still scarce, but observational studies as well as two RCTs support the hypothesis that exercise contributes to increased peak bone mass in adolescents and young adults (Category B)[5,15].

Blood lipids and lipoproteins

Based on data from 51 individual studies (including 28 RCTs) with exercise training programs of ≥ 12 weeks, the most common lipid change (40% of the studies)

was an increase of high-density lipoprotein (HDL) cholesterol levels (4.6% on the average) both in men and women. Reductions in low-density lipoprotein (LDL) cholesterol and triglyceride levels were also reported, although less frequently than changes in HDL levels[9]. The evidence for the plasma lipid and lipoprotein profile-improving effects of moderate to hard intensity exercise was found to be strong enough to warrant Category B classification. However, only a few studies have addressed the dose-response effect of increasing exercise intensity on blood lipids and the results are conflicting[5]. There is some evidence that pre-training lipid levels and changes in body composition may contribute to the training-induced changes in lipid levels.

Hemostatic factors

The contribution of the hemostatic system (platelet aggregation, coagulation and fibrinolysis) to cardiovascular disease risk, especially to sudden cardiac events, has received a lot of attention during the last decade. Intensive acute exercise has been shown to activate both coagulation promoting factors as well as fibrinolytic system, the effect on coagulation being greater in sedentary subjects. The effect of exercise training on hemostatic factors is best documented for platelet functions. Regular physical activity decreases platelet adhesiveness and aggregation at rest and during acute strenuous exercise and the evidence was considered to be of Category B[10]. However, an assessment of the dose-response relationship from these data was not possible. Data on the effects of physical activity on plasma fibrinogen, tissue plasminogen activator (t-PA) and its inhibitor (PAI-1) levels are mainly based on observational studies and the few available intervention studies have yielded conflicting results (Category C)[10]. In summary, the presently available research suggests that there is no evidence for a dose-response relationship between physical activity and hemostatic factors[5].

Others

Low back pain and osteoarthritis

The evidence for the beneficial effects of physical activity on low back pain was found to be conflicting[15]. Two RTCs have reported that leisure time activities may prevent the first occurrence low back problems, whereas prolonged occupational and sports activities increase the risk (evidence Category B). Even though exercise is considered useful as a component of an active rehabilitation program, there is no evidence that specific exercises are beneficial for secondary prevention. Likewise, supervised exercise may be effective in the rehabilitation of patients with osteoarthritis of the knee. There is no evidence available for a preventive effect of physical activity on osteoarthritis in weight-bearing joints. In fact, heavy occupational and sports activities may even increase the risk of osteoarthritis (Category C)[15]. Physical activity appears to have both beneficial and detrimental effects on low back pain and osteoarthritis. The available data do not allow a conclusion on dose-response relationships[5].

Quality of life and independent living in the elderly, depression and anxiety

The evidence for a role of physical activity on quality of life and independent living among the elderly, and depression and anxiety was considered to be of Category C[2,12]. Cross-sectional studies have indicated that physical activity is positively associated with overall well-being and physical function. Intervention studies provide some support for the latter observation whereas the results are inconclusive for overall well-being[12]. Observational studies suggest that physically active individuals are less likely to develop depressive illnesses than their sedentary counterparts. Short-term (6-12 weeks) intervention studies in patients with mild to moderate depression and anxiety have shown that aerobic exercise induces an improvement of symptoms comparable to those with some pharmacological agents, although the response may be slower (Category B)[2]. At this time, there is only Category C evidence for a dose-response relationship between physical activity and improvement in activity in daily living in the elderly, whereas no evidence of dose-response was found between physical activity and depression and anxiety[5].

Summary and Conclusions

There is ample evidence supporting the beneficial effects of regular physical activity on all reviewed health outcomes. There is a strong suggestion of an inverse and linear relationship between regular physical activity and rates of all-cause mortality, total CVD and coronary heart disease incidence and mortality, and incidence of type 2 diabetes mellitus. However, for other health outcomes, the dose-response relationship with physical activity was less clear (Table 2). Five reasons have been cited to account for this situation[5]:

1. The absence of studies focusing on dose-response issues;
2. Lack of field methods sensitive and accurate enough to quantify the dose of physical activity;
3. Small effects of physical activity on some health outcomes;
4. Uncontrolled confounding factors such as genetic variability;
5. Simultaneous changes in body weight and composition that accompany physical activity.

In cases in which a dose-response relationship cannot be proven, the emphasis should be on the level of physical activity or fitness that results in a beneficial effect[5]. It is also important to consider the potential health risks associated with regular physical activity. As the intensity and volume of exercise increase, the risk of injury and harm, especially musculoskeletal for most individuals and cardiovascular for those with underlying disease, becomes greater. The intensity of exercise is particularly critical because it is a major contributor to exercise-induced medical complications. The assessment of dose-response relationships should therefore consider both the exercise dose that induces the greatest health benefits and the potential risks in a particular population[5].

The limited number of RCTs is the most serious obstacle in the effort to define dose relationships between physical activity and health outcomes. There is, therefore, a pressing need for large randomized controlled trials on the effect of multiple levels and patterns of physical activity on a range of health outcomes and risks.

Table 2.
Summary of the dose-response evidence for various health outcomes

Health outcome	Dose-response relationship	Evidence category
All-Cause Mortality	Yes	C
Cardiovascular Disease	Yes	C
Type 2 diabetes mellitus	Yes	C
Cancer	Yes	C (colon cancer)
Blood pressure and hypertension	No	A (moderate intensity)
		B (high intensity)
Blood lipids and lipoproteins	No	B
Overweight, obesity, fat distribution	Yes	A (short-term weight loss)
	No	B (visceral fat loss)
	No	C (prevention of weight gain over time)
Coagulation and hemostatic factors	No	B (platelet aggregation)
	No	B (acute exercise and fibrinolysis)
	No	C (regular exercise and fibrinolysis)
Low back pain	No	B (primary prevention)
	No	C (secondary prevention)
Osteoarthritis	No	C
Osteoporosis	No	A (maintenance of peak bone mass in premenopausal women and prevention of bone loss after menopause)
	No	B (increased peak bone mass)
Quality of life and independent living in the elderly	Yes	C
Depression and anxiety	No	B

There is ample evidence supporting the beneficial effects of regular physical activity on all reviewed health outcomes.

There is a strong suggestion of an inverse and linear relationship between regular physical activity and rates of all-cause mortality, total CVD and coronary heart disease incidence and mortality, and incidence of type 2 diabetes mellitus. However, for other health outcomes, the dose-response relationship with physical activity was less clear.

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